

# SEQUENCE LISTING

<110> Nicolaides, Nicholas C  
 Sass, Philip M  
 Grasso, Luigi M  
 Kline, J Bradford

<120> METHODS FOR GENERATING ANTIBIOTIC RESISTANT MICROBES AND NOVEL  
 ANTIBIOTICS

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**A**



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Ser Cys Asn Lys Lys Ser Asn Val Ile Asp Asn Lys Ser Gly Lys Val  
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Thr Ala Tyr Asp Leu Leu Ser Asn Arg Val Ile Lys Lys Pro Met Ser  
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Gln Glu Ser Gln Met Ser Leu Lys Asp Gly Arg Lys Lys Ile Lys Pro  
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Ser Asn Gln Pro Lys Leu Asp Glu Leu Leu Gln Ser Gln Ile Glu Lys  
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Arg Arg Ser Gln Asn Ile Lys Met Val Gln Ile Pro Phe Ser Met Lys  
690 695 700

Asn Leu Lys Ile Asn Phe Lys Lys Gln Asn Lys Val Asp Leu Glu Glu  
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Lys Asp Glu Pro Cys Leu Ile His Asn Leu Arg Phe Pro Asp Ala Trp  
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Leu Met Thr Ser Lys Thr Glu Val Met Leu Leu Asn Pro Tyr Arg Val  
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Glu Glu Ala Leu Leu Phe Lys Arg Leu Leu Glu Asn His Lys Leu Pro  
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Ala Glu Pro Leu Glu Lys Pro Ile Met Leu Thr Glu Ser Leu Phe Asn  
770 775 780

Gly Ser His Tyr Leu Asp Val Leu Tyr Lys Met Thr Ala Asp Asp Gln  
785 790 795 800

Arg Tyr Ser Gly Ser Thr Tyr Leu Ser Asp Pro Arg Leu Thr Ala Asn  
805 810 815

Gly Phe Lys Ile Lys Leu Ile Pro Gly Val Ser Ile Thr Glu Asn Tyr  
820 825 830

Leu Glu Ile Glu Gly Met Ala Asn Cys Leu Pro Phe Tyr Gly Val Ala  
835 840 845

Asp Leu Lys Glu Ile Leu Asn Ala Ile Leu Asn Arg Asn Ala Lys Glu  
850 855 860

Val Tyr Glu Cys Arg Pro Arg Lys Val Ile Ser Tyr Leu Glu Gly Glu  
865 870 875 880

Ala Val Arg Leu Ser Arg Gln Leu Pro Met Tyr Leu Ser Lys Glu Asp  
885 890 895

Ile Gln Asp Ile Ile Tyr Arg Met Lys His Gln Phe Gly Asn Glu Ile  
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Phe Asp Lys Ile Glu Val Arg Asp Asn Gly Glu Gly Ile Lys Ala Val  
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Asp Ala Pro Val Met Ala Met Lys Tyr Tyr Thr Ser Lys Ile Asn Ser  
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His Glu Asp Leu Glu Asn Leu Thr Thr Tyr Gly Phe Arg Gly Glu Ala

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Tyr Gly Pro Leu Pro Ser Thr Asn Ser Tyr Glu Asn Asn Lys Thr Asp

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Asn Pro Lys Thr Ser Leu Glu Asp Ala Thr Leu Gln Ile Glu Glu Leu

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600

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Trp Lys Thr Leu Ser Glu Glu Glu Lys Leu Lys Tyr Glu Glu Lys Ala  
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Thr Lys Asp Leu Glu Arg Tyr Asn Ser Gln Met Lys Arg Ala Ile Glu  
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Gln Glu Ser Gln Met Ser Leu Lys Asp Gly Arg Lys Lys Ile Lys Pro  
645 650 655

Thr Ser Ala Trp Asn Leu Ala Gln Lys His Lys Leu Lys Thr Ser Leu  
660 665 670

Ser Asn Gln Pro Lys Leu Asp Glu Leu Leu Gln Ser Gln Ile Glu Lys  
675 680 685

Arg Arg Ser Gln Asn Ile Lys Met Val Gln Ile Pro Phe Ser Met Lys  
690 695 700

Asn Leu Lys Ile Asn Phe Lys Lys Gln Asn Lys Val Asp Leu Glu Glu  
705 710 715 720

Lys Asp Glu Pro Cys Leu Ile His Asn Leu Arg Phe Pro Asp Ala Trp  
725 730 735

Leu Met Thr Ser Lys Thr Glu Val Met Leu Leu Asn Pro Tyr Arg Val  
740 745 750

Glu Glu Ala Leu Leu Phe Lys Arg Leu Leu Glu Asn His Lys Leu Pro  
755 760 765

Ala Glu Pro Leu Glu Lys Pro Ile Met Leu Thr Glu Ser Leu Phe Asn  
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Gly Ser His Tyr Leu Asp Val Leu Tyr Lys Met Thr Ala Asp Asp Gln  
785 790 795 800

Arg Tyr Ser Gly Ser Thr Tyr Leu Ser Asp Pro Arg Leu Thr Ala Asn  
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Gly Phe Lys Ile Lys Leu Ile Pro Gly Val Ser Ile Thr Glu Asn Tyr  
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Leu Glu Ile Glu Gly Met Ala Asn Cys Leu Pro Phe Tyr Gly Val Ala  
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Asp Leu Lys Glu Ile Leu Asn Ala Ile Leu Asn Arg Asn Ala Lys Glu

850

855

860

Val Tyr Glu Cys Arg Pro Arg Lys Val Ile Ser Tyr Leu Glu Gly Glu  
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Ala Val Arg Leu Ser Arg Gln Leu Pro Met Tyr Leu Ser Lys Glu Asp  
885 890 895

Ile Gln Asp Ile Ile Tyr Arg Met Lys His Gln Phe Gly Asn Glu Ile  
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35 40 45

Asp Ala Leu Leu Ala Ala Arg Glu Val Phe Lys Thr Gln Gly Val Ile  
50 55 60

Lys Tyr Met Gly Pro Ala Gly Ala Lys Asn Leu Gln Ser Val Val Leu  
65 70 75 80

Ser Lys Met Asn Phe Glu Ser Phe Val Lys Asp Leu Leu Leu Val Arg  
85 90 95

Gln Tyr Arg Val Glu Val Tyr Lys Asn Arg Ala Gly Asn Lys Ala Ser  
100 105 110

Lys Glu Asn Asp Trp Tyr Leu Ala Tyr Lys Ala Ser Pro Gly Asn Leu  
115 120 125

Ser Gln Phe Glu Asp Ile Leu Phe Gly Asn Asn Asp Met Ser Ala Ser  
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Ile Gly Val Val Gly Val Lys Met Ser Ala Val Asp Gly Gln Arg Gln  
145 150 155 160

Val Gly Val Gly Tyr Val Asp Ser Ile Gln Arg Lys Leu Gly Leu Cys  
165 170 175

Glu Phe Pro Asp Asn Asp Gln Phe Ser Asn Leu Glu Ala Leu Leu Ile  
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Gln Ile Gly Pro Lys Glu Cys Val Leu Pro Gly Gly Glu Thr Ala Gly

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205

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Gln Thr Leu Asn Asp Val Leu Ala Gln Leu Asp Ala Val Val Ser Phe 595 600 605		
Ala His Val Ser Asn Gly Ala Pro Val Pro Tyr Val Arg Pro Ala Ile 610 615 620		
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Cys Val Glu Val Gln Asp Glu Ile Ala Phe Ile Pro Asn Asp Val Tyr 645 650 655		
Phe Glu Lys Asp Lys Gln Met Phe His Ile Ile Thr Gly Pro Asn Met 660 665 670		
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 Gly Thr Ser Thr Tyr Asp Gly Phe Gly Leu Ala Trp Ala Ile Ser Glu  
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 Tyr Ile Ala Thr Lys Ile Gly Ala Phe Cys Met Phe Ala Thr His Phe  
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 His Glu Leu Thr Ala Leu Ala Asn Gln Ile Pro Thr Val Asn Asn Leu  
                              785                               790                               795                               800  
 His Val Thr Ala Leu Thr Thr Glu Glu Thr Leu Thr Met Leu Tyr Gln  
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                              820                               825                               830  
 Leu Ala Asn Phe Pro Lys His Val Ile Glu Cys Ala Lys Gln Lys Ala  
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 Leu Glu Leu Glu Glu Phe Gln Tyr Ile Gly Glu Ser Gln Gly Tyr Asp  
                              850                               855                               860  
 Ile Met Glu Pro Ala Ala Lys Lys Cys Tyr Leu Glu Arg Glu Gln Gly  
                              865                               870                               875                               880  
 Glu Lys Ile Ile Gln Glu Phe Leu Ser Lys Val Lys Gln Met Pro Phe  
                              885                               890                               895  
 Thr Glu Met Ser Glu Glu Asn Ile Thr Ile Lys Leu Lys Gln Leu Lys  
                              900                               905                               910  
 Ala Glu Val Ile Ala Lys Asn Asn Ser Phe Val Asn Glu Ile Ile Ser  
                              915                               920                               925  
 Arg Ile Lys Val Thr Thr  
                              930

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 <212> DNA  
 <213> Homo sapiens

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 ctcagtttag aaatcagtc ccagaatgtg gatgttaatg tgcacccac aaagcatgaa 960  
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aataaataga tgtgtcttaa cata 2484

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<212> PRT
<213> Homo sapiens

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<400> 12

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Asn Arg Ile Ala Ala Gly Glu Val Ile Gln Arg Pro Ala Asn Ala Ile
          20          25          30

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Lys Glu Met Ile Glu Asn Cys Leu Asp Ala Lys Ser Thr Ser Ile Gln
          35          40          45

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Val Ile Val Lys Glu Gly Gly Leu Lys Leu Ile Gln Ile Gln Asp Asn
          50          55          60

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Gly Thr Gly Ile Arg Lys Glu Asp Leu Asp Ile Val Cys Glu Arg Phe
65          70          75          80

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Thr Thr Ser Lys Leu Gln Ser Phe Glu Asp Leu Ala Ser Ile Ser Thr
          85          90          95

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Tyr Gly Phe Arg Gly Glu Ala Leu Ala Ser Ile Ser His Val Ala His
          100          105          110

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Val Thr Ile Thr Thr Lys Thr Ala Asp Gly Lys Cys Ala Tyr Arg Ala
          115          120          125

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Ser Tyr Ser Asp Gly Lys Leu Lys Ala Pro Pro Lys Pro Cys Ala Gly
          130          135          140

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Asn Gln Gly Thr Gln Ile Thr Val Glu Asp Leu Phe Tyr Asn Ile Ala  
145 150 155 160

Thr Arg Arg Lys Ala Leu Lys Asn Pro Ser Glu Glu Tyr Gly Lys Ile  
165 170 175

Leu Glu Val Val Gly Arg Tyr Ser Val His Asn Ala Gly Ile Ser Phe  
180 185 190

Ser Val Lys Lys Gln Gly Glu Thr Val Ala Asp Val Arg Thr Leu Pro  
195 200 205

Asn Ala Ser Thr Val Asp Asn Ile Arg Ser Ile Phe Gly Asn Ala Val  
210 215 220

Ser Arg Glu Leu Ile Glu Ile Gly Cys Glu Asp Lys Thr Leu Ala Phe  
225 230 235 240

Lys Met Asn Gly Tyr Ile Ser Asn Ala Asn Tyr Ser Val Lys Lys Cys  
245 250 255

Ile Phe Leu Leu Phe Ile Asn His Arg Leu Val Glu Ser Thr Ser Leu  
260 265 270

Arg Lys Ala Ile Glu Thr Val Tyr Ala Ala Tyr Leu Pro Lys Asn Thr  
275 280 285

His Pro Phe Leu Tyr Leu Ser Leu Glu Ile Ser Pro Gln Asn Val Asp  
290 295 300

Val Asn Val His Pro Thr Lys His Glu Val His Phe Leu His Glu Glu  
305 310 315 320

Ser Ile Leu Glu Arg Val Gln Gln His Ile Glu Ser Lys Leu Leu Gly  
325 330 335

Ser Asn Ser Ser Arg Met Tyr Phe Thr Gln Thr Leu Leu Pro Gly Leu  
340 345 350

Ala Gly Pro Ser Gly Glu Met Val Lys Ser Thr Thr Ser Leu Thr Ser  
355 360 365

Ser Ser Thr Ser Gly Ser Ser Asp Lys Val Tyr Ala His Gln Met Val  
370 375 380

Arg Thr Asp Ser Arg Glu Gln Lys Leu Asp Ala Phe Leu Gln Pro Leu  
385 390 395 400

Ser Lys Pro Leu Ser Ser Gln Pro Gln Ala Ile Val Thr Glu Asp Lys  
 405 410 415

Thr Asp Ile Ser Ser Gly Arg Ala Arg Gln Gln Asp Glu Glu Met Leu  
 420 425 430

Glu Leu Pro Ala Pro Ala Glu Val Ala Ala Lys Asn Gln Ser Leu Glu  
 435 440 445

Gly Asp Thr Thr Lys Gly Thr Ser Glu Met Ser Glu Lys Arg Gly Pro  
 450 455 460

Thr Ser Ser Asn Pro Arg Lys Arg His Arg Glu Asp Ser Asp Val Glu  
 465 470 475 480

Met Val Glu Asp Asp Ser Arg Lys Glu Met Thr Ala Ala Cys Thr Pro  
 485 490 495

Arg Arg Arg Ile Ile Asn Leu Thr Ser Val Leu Ser Leu Gln Glu Glu  
 500 505 510

Ile Asn Glu Gln Gly His Glu Val Leu Arg Glu Met Leu His Asn His  
 515 520 525

Ser Phe Val Gly Cys Val Asn Pro Gln Trp Ala Leu Ala Gln His Gln  
 530 535 540

Thr Lys Leu Tyr Leu Leu Asn Thr Thr Lys Leu Ser Glu Glu Leu Phe  
 545 550 555 560

Tyr Gln Ile Leu Ile Tyr Asp Phe Ala Asn Phe Gly Val Leu Arg Leu  
 565 570 575

Ser Glu Pro Ala Pro Leu Phe Asp Leu Ala Met Leu Ala Leu Asp Ser  
 580 585 590

Pro Glu Ser Gly Trp Thr Glu Glu Asp Gly Pro Lys Glu Gly Leu Ala  
 595 600 605

Glu Tyr Ile Val Glu Phe Leu Lys Lys Lys Ala Glu Met Leu Ala Asp  
 610 615 620

Tyr Phe Ser Leu Glu Ile Asp Glu Glu Gly Asn Leu Ile Gly Leu Pro  
 625 630 635 640

Leu Leu Ile Asp Asn Tyr Val Pro Pro Leu Glu Gly Leu Pro Ile Phe  
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Ile Leu Arg Leu Ala Thr Glu Val Asn Trp Asp Glu Glu Lys Glu Cys  
660 665 670

Phe Glu Ser Leu Ser Lys Glu Cys Ala Met Phe Tyr Ser Ile Arg Lys  
675 680 685

Gln Tyr Ile Ser Glu Glu Ser Thr Leu Ser Gly Gln Gln Ser Glu Val  
690 695 700

Pro Gly Ser Ile Pro Asn Ser Trp Lys Trp Thr Val Glu His Ile Val  
705 710 715 720

Tyr Lys Ala Leu Arg Ser His Ile Leu Pro Pro Lys His Phe Thr Glu  
725 730 735

Asp Gly Asn Ile Leu Gln Leu Ala Asn Leu Pro Asp Leu Tyr Lys Val  
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Phe Glu Arg Cys  
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caagagtttg ccgacctaac tcaggttgaa acttttggct ttcgggggga agctctgagc 360  
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<210> 14  
<211> 133  
<212> PRT  
<213> Homo sapiens

<400> 14

Met Lys Gln Leu Pro Ala Ala Thr Val Arg Leu Leu Ser Ser Ser Gln  
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Ile Ile Thr Ser Val Val Ser Val Val Lys Glu Leu Ile Glu Asn Ser



20

25

30

Leu Asp Ala Gly Ala Thr Ser Val Asp Val Lys Leu Glu Asn Tyr Gly  
35 40 45

Phe Asp Lys Ile Glu Val Arg Asp Asn Gly Glu Gly Ile Lys Ala Val  
50 55 60

Asp Ala Pro Val Met Ala Met Lys Tyr Tyr Thr Ser Lys Ile Asn Ser  
65 70 75 80

His Glu Asp Leu Glu Asn Leu Thr Thr Tyr Gly Phe Arg Gly Glu Ala  
85 90 95

Leu Gly Ser Ile Cys Cys Ile Ala Glu Val Leu Ile Thr Thr Arg Thr  
100 105 110

Ala Ala Asp Asn Phe Ser Thr Gln Tyr Val Leu Asp Gly Ser Gly His  
115 120 125

Ile Leu Ser Gln Lys  
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atga 4264

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<211> 1360  
<212> PRT  
<213> Homo sapiens

<400> 16

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20 25 30

Arg Ala Ala Ala Ala Pro Gly Ala Ser Pro Ser Pro Gly Gly Asp Ala  
35 40 45

Ala Trp Ser Glu Ala Gly Pro Gly Pro Arg Pro Leu Ala Arg Ser Ala  
50 55 60

Ser Pro Pro Lys Ala Lys Asn Leu Asn Gly Gly Leu Arg Arg Ser Val  
65 70 75 80

Ala Pro Ala Ala Pro Thr Ser Cys Asp Phe Ser Pro Gly Asp Leu Val  
85 90 95

Trp Ala Lys Met Glu Gly Tyr Pro Trp Trp Pro Cys Leu Val Tyr Asn  
100 105 110

His Pro Phe Asp Gly Thr Phe Ile Arg Glu Lys Gly Lys Ser Val Arg  
115 120 125

Val His Val Gln Phe Phe Asp Asp Ser Pro Thr Arg Gly Trp Val Ser  
130 135 140

Lys Arg Leu Leu Lys Pro Tyr Thr Gly Ser Lys Ser Lys Glu Ala Gln  
145 150 155 160

Lys Gly Gly His Phe Tyr Ser Ala Lys Pro Glu Ile Leu Arg Ala Met  
165 170 175

Gln Arg Ala Asp Glu Ala Leu Asn Lys Asp Lys Ile Lys Arg Leu Glu  
180 185 190

Leu Ala Val Cys Asp Glu Pro Ser Glu Pro Glu Glu Glu Glu Glu Met  
195 200 205

Glu Val Gly Thr Thr Tyr Val Thr Asp Lys Ser Glu Glu Asp Asn Glu  
210 215 220

Ile Glu Ser Glu Glu Glu Val Gln Pro Lys Thr Gln Gly Ser Arg Arg  
225 230 235 240

Ser Ser Arg Gln Ile Lys Lys Arg Arg Val Ile Ser Asp Ser Glu Ser  
245 250 255

Asp Ile Gly Gly Ser Asp Val Glu Phe Lys Pro Asp Thr Lys Glu Glu  
260 265 270

Gly Ser Ser Asp Glu Ile Ser Ser Gly Val Gly Asp Ser Glu Ser Glu  
275 280 285

Gly Leu Asn Ser Pro Val Lys Val Ala Arg Lys Arg Lys Arg Met Val  
290 295 300

Thr Gly Asn Gly Ser Leu Lys Arg Lys Ser Ser Arg Lys Glu Thr Pro  
305 310 315 320

Ser Ala Thr Lys Gln Ala Thr Ser Ile Ser Ser Glu Thr Lys Asn Thr  
325 330 335

Leu Arg Ala Phe Ser Ala Pro Gln Asn Ser Glu Ser Gln Ala His Val  
340 345 350

Ser Gly Gly Gly Asp Asp Ser Ser Arg Pro Thr Val Trp Tyr His Glu  
355 360 365

Thr Leu Glu Trp Leu Lys Glu Glu Lys Arg Arg Asp Glu His Arg Arg  
370 375 380

Arg Pro Asp His Pro Asp Phe Asp Ala Ser Thr Leu Tyr Val Pro Glu  
385 390 395 400

Asp Phe Leu Asn Ser Cys Thr Pro Gly Met Arg Lys Trp Trp Gln Ile  
405 410 415

Lys Ser Gln Asn Phe Asp Leu Val Ile Cys Tyr Lys Val Gly Lys Phe  
420 425 430

Tyr Glu Leu Tyr His Met Asp Ala Leu Ile Gly Val Ser Glu Leu Gly  
435 440 445

Leu Val Phe Met Lys Gly Asn Trp Ala His Ser Gly Phe Pro Glu Ile  
450 455 460

Ala Phe Gly Arg Tyr Ser Asp Ser Leu Val Gln Lys Gly Tyr Lys Val  
465 470 475 480

Ala Arg Val Glu Gln Thr Glu Thr Pro Glu Met Met Glu Ala Arg Cys  
485 490 495

Arg Lys Met Ala His Ile Ser Lys Tyr Asp Arg Val Val Arg Arg Glu  
500 505 510

Ile Cys Arg Ile Ile Thr Lys Gly Thr Gln Thr Tyr Ser Val Leu Glu  
515 520 525

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Gly Asp Pro Ser Glu Asn Tyr Ser Lys Tyr Leu Leu Ser Leu Lys Glu  
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Lys Glu Glu Asp Ser Ser Gly His Thr Arg Ala Tyr Gly Val Cys Phe  
545 550 555 560

Val Asp Thr Ser Leu Gly Lys Phe Phe Ile Gly Gln Phe Ser Asp Asp  
565 570 575

Arg His Cys Ser Arg Phe Arg Thr Leu Val Ala His Tyr Pro Pro Val  
580 585 590

Gln Val Leu Phe Glu Lys Gly Asn Leu Ser Lys Glu Thr Lys Thr Ile  
595 600 605

Leu Lys Ser Ser Leu Ser Cys Ser Leu Gln Glu Gly Leu Ile Pro Gly  
610 615 620

Ser Gln Phe Trp Asp Ala Ser Lys Thr Leu Arg Thr Leu Leu Glu Glu  
625 630 635 640

Glu Tyr Phe Arg Glu Lys Leu Ser Asp Gly Ile Gly Val Met Leu Pro  
645 650 655

Gln Val Leu Lys Gly Met Thr Ser Glu Ser Asp Ser Ile Gly Leu Thr  
660 665 670

Pro Gly Glu Lys Ser Glu Leu Ala Leu Ser Ala Leu Gly Gly Cys Val  
675 680 685

Phe Tyr Leu Lys Lys Cys Leu Ile Asp Gln Glu Leu Leu Ser Met Ala  
690 695 700

Asn Phe Glu Glu Tyr Ile Pro Leu Asp Ser Asp Thr Val Ser Thr Thr  
705 710 715 720

Arg Ser Gly Ala Ile Phe Thr Lys Ala Tyr Gln Arg Met Val Leu Asp  
725 730 735

Ala Val Thr Leu Asn Asn Leu Glu Ile Phe Leu Asn Gly Thr Asn Gly  
740 745 750

Ser Thr Glu Gly Thr Leu Leu Glu Arg Val Asp Thr Cys His Thr Pro  
755 760 765

Phe Gly Lys Arg Leu Leu Lys Gln Trp Leu Cys Ala Pro Leu Cys Asn  
770 775 780

His Tyr Ala Ile Asn Asp Arg Leu Asp Ala Ile Glu Asp Leu Met Val  
785 790 795 800

Val Pro Asp Lys Ile Ser Glu Val Val Glu Leu Leu Lys Lys Leu Pro  
805 810 815

Asp Leu Glu Arg Leu Leu Ser Lys Ile His Asn Val Gly Ser Pro Leu  
820 825 830

Lys Ser Gln Asn His Pro Asp Ser Arg Ala Ile Met Tyr Glu Glu Thr  
835 840 845

Thr Tyr Ser Lys Lys Lys Ile Ile Asp Phe Leu Ser Ala Leu Glu Gly  
850 855 860

Phe Lys Val Met Cys Lys Ile Ile Gly Ile Met Glu Glu Val Ala Asp  
865 870 875 880

Gly Phe Lys Ser Lys Ile Leu Lys Gln Val Ile Ser Leu Gln Thr Lys  
885 890 895

Asn Pro Glu Gly Arg Phe Pro Asp Leu Thr Val Glu Leu Asn Arg Trp  
900 905 910

Asp Thr Ala Phe Asp His Glu Lys Ala Arg Lys Thr Gly Leu Ile Thr  
915 920 925

Pro Lys Ala Gly Phe Asp Ser Asp Tyr Asp Gln Ala Leu Ala Asp Ile  
930 935 940

Arg Glu Asn Glu Gln Ser Leu Leu Glu Tyr Leu Glu Lys Gln Arg Asn  
945 950 955 960

Arg Ile Gly Cys Arg Thr Ile Val Tyr Trp Gly Ile Gly Arg Asn Arg  
965 970 975

Tyr Gln Leu Glu Ile Pro Glu Asn Phe Thr Thr Arg Asn Leu Pro Glu  
980 985 990

Glu Tyr Glu Leu Lys Ser Thr Lys Lys Gly Cys Lys Arg Tyr Trp Thr  
995 1000 1005

Lys Thr Ile Glu Lys Lys Leu Ala Asn Leu Ile Asn Ala Glu Glu  
1010 1015 1020

Arg Arg Asp Val Ser Leu Lys Asp Cys Met Arg Arg Leu Phe Tyr  
1025 1030 1035

Asn	Phe	Asp	Lys	Asn	Tyr	Lys	Asp	Trp	Gln	Ser	Ala	Val	Glu	Cys
1040						1045					1050			
Ile	Ala	Val	Leu	Asp	Val	Leu	Leu	Cys	Leu	Ala	Asn	Tyr	Ser	Arg
1055						1060					1065			
Gly	Gly	Asp	Gly	Pro	Met	Cys	Arg	Pro	Val	Ile	Leu	Leu	Pro	Glu
1070						1075					1080			
Asp	Thr	Pro	Pro	Phe	Leu	Glu	Leu	Lys	Gly	Ser	Arg	His	Pro	Cys
1085						1090					1095			
Ile	Thr	Lys	Thr	Phe	Phe	Gly	Asp	Asp	Phe	Ile	Pro	Asn	Asp	Ile
1100						1105					1110			
Leu	Ile	Gly	Cys	Glu	Glu	Glu	Glu	Gln	Glu	Asn	Gly	Lys	Ala	Tyr
1115						1120					1125			
Cys	Val	Leu	Val	Thr	Gly	Pro	Asn	Met	Gly	Gly	Lys	Ser	Thr	Leu
1130						1135					1140			
Met	Arg	Gln	Ala	Gly	Leu	Leu	Ala	Val	Met	Ala	Gln	Met	Gly	Cys
1145						1150					1155			
Tyr	Val	Pro	Ala	Glu	Val	Cys	Arg	Leu	Thr	Pro	Ile	Asp	Arg	Val
1160						1165					1170			
Phe	Thr	Arg	Leu	Gly	Ala	Ser	Asp	Arg	Ile	Met	Ser	Gly	Glu	Ser
1175						1180					1185			
Thr	Phe	Phe	Val	Glu	Leu	Ser	Glu	Thr	Ala	Ser	Ile	Leu	Met	His
1190						1195					1200			
Ala	Thr	Ala	His	Ser	Leu	Val	Leu	Val	Asp	Glu	Leu	Gly	Arg	Gly
1205						1210					1215			
Thr	Ala	Thr	Phe	Asp	Gly	Thr	Ala	Ile	Ala	Asn	Ala	Val	Val	Lys
1220						1225					1230			
Glu	Leu	Ala	Glu	Thr	Ile	Lys	Cys	Arg	Thr	Leu	Phe	Ser	Thr	His
1235						1240					1245			
Tyr	His	Ser	Leu	Val	Glu	Asp	Tyr	Ser	Gln	Asn	Val	Ala	Val	Arg
1250						1255					1260			
Leu	Gly	His	Met	Ala	Cys	Met	Val	Glu	Asn	Glu	Cys	Glu	Asp	Pro
1265						1270					1275			



Ser Gln Glu Thr Ile Thr Phe Leu Tyr Lys Phe Ile Lys Gly Ala  
1280 1285 1290

Cys Pro Lys Ser Tyr Gly Phe Asn Ala Ala Arg Leu Ala Asn Leu  
1295 1300 1305

Pro Glu Glu Val Ile Gln Lys Gly His Arg Lys Ala Arg Glu Phe  
1310 1315 1320

Glu Lys Met Asn Gln Ser Leu Arg Leu Phe Arg Glu Val Cys Leu  
1325 1330 1335

Ala Ser Glu Arg Ser Thr Val Asp Ala Glu Ala Val His Lys Leu  
1340 1345 1350

Leu Thr Leu Ile Lys Glu Leu  
1355 1360

<210> 17  
<211> 1408  
<212> DNA  
<213> Homo sapiens

<400> 17  
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ggctttacct ggtacatcgg catggcgcaa ccaaagcaag agagggtggc gcgtgccaga 180  
caccaacggt cggaaaccgc cagacaccaa cggtcggaaa ccgccaagac accaacgctc 240  
ggaaaccgcc agacaccaac gctcggaaac cgccagacac caaggctcgg aatccacgcc 300  
aggccacgac ggagggcgac tacctccctt ctgaccctgc tgctggcgtt cggaaaaaac 360  
gcagtccggt gtgctctgat tgggccaggc tctttgacgt cacggactcg acctttgaca 420  
gagccactag gcgaaaagga gagacgggaa gtattttttc cgccccgcc ggaaaggggtg 480  
gagcacaacg tcgaaagcag ccgttgggag ccaggaggc ggggcgcctg tgggagccgt 540  
ggaggggaact ttcccagtc cagaggcgga tccggtgttg catccttgga gcgagctgag 600  
aactcgagta cagaacctgc taaggccatc aaacctattg atcggaagtc agtccatcag 660  
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cagaaaaccc cctacccccg cccagaggg atgacagtca gcgtgaagca attattttct 1080  
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aatccaaaaa aaaaaaaaaa aaaaaaaaaa 1408

<210> 18  
<211> 389  
<212> PRT  
<213> Homo sapiens

<400> 18

Met Ala Gln Pro Lys Gln Glu Arg Val Ala Arg Ala Arg His Gln Arg  
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Ser Glu Thr Ala Arg His Gln Arg Ser Glu Thr Ala Lys Thr Pro Thr  
20 25 30

Leu Gly Asn Arg Gln Thr Pro Thr Leu Gly Asn Arg Gln Thr Pro Arg  
35 40 45

Leu Gly Ile His Ala Arg Pro Arg Arg Arg Ala Thr Thr Ser Leu Leu  
50 55 60

Thr Leu Leu Leu Ala Phe Gly Lys Asn Ala Val Arg Cys Ala Leu Ile  
65 70 75 80

Gly Pro Gly Ser Leu Thr Ser Arg Thr Arg Pro Leu Thr Glu Pro Leu  
85 90 95

Gly Glu Lys Glu Arg Arg Glu Val Phe Phe Pro Pro Arg Pro Glu Arg  
100 105 110

Val Glu His Asn Val Glu Ser Ser Arg Trp Glu Pro Arg Arg Arg Gly  
115 120 125

Ala Cys Gly Ser Arg Gly Gly Asn Phe Pro Ser Pro Arg Gly Gly Ser  
130 135 140

Gly Val Ala Ser Leu Glu Arg Ala Glu Asn Ser Ser Thr Glu Pro Ala  
145 150 155 160

Lys Ala Ile Lys Pro Ile Asp Arg Lys Ser Val His Gln Ile Cys Ser

00943597072504

165

170

175

Gly Pro Val Val Pro Ser Leu Arg Pro Asn Ala Val Lys Glu Leu Val  
180 185 190

Glu Asn Ser Leu Asp Ala Gly Ala Thr Asn Val Asp Leu Lys Leu Lys  
195 200 205

Asp Tyr Gly Val Asp Leu Ile Glu Val Ser Gly Asn Gly Cys Gly Val  
210 215 220

Glu Glu Glu Asn Phe Glu Gly Phe Thr Leu Lys His His Thr Cys Lys  
225 230 235 240

Ile Gln Glu Phe Ala Asp Leu Thr Gln Val Glu Thr Phe Gly Phe Arg  
245 250 255

Gly Glu Ala Leu Ser Ser Leu Cys Ala Leu Ser Asp Val Thr Ile Ser  
260 265 270

Thr Cys Arg Val Ser Ala Lys Val Gly Thr Arg Leu Val Phe Asp His  
275 280 285

Tyr Gly Lys Ile Ile Gln Lys Thr Pro Tyr Pro Arg Pro Arg Gly Met  
290 295 300

Thr Val Ser Val Lys Gln Leu Phe Ser Thr Leu Pro Val His His Lys  
305 310 315 320

Glu Phe Gln Arg Asn Ile Lys Lys Lys Arg Ala Cys Phe Pro Phe Ala  
325 330 335

Phe Cys Arg Asp Cys Gln Phe Pro Glu Ala Ser Pro Ala Met Leu Pro  
340 345 350

Val Gln Pro Val Glu Leu Thr Pro Arg Ser Thr Pro Pro His Pro Cys  
355 360 365

Ser Leu Glu Asp Asn Val Ile Thr Val Phe Ser Ser Val Lys Asn Gly  
370 375 380

Pro Gly Ser Ser Arg  
385

<210> 19  
<211> 1785  
<212> DNA  
<213> Homo sapiens

<400> 19  
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 gggagctgca gaccagtctt ccgtggcagg ctgagcgcct cagtcttcag tagggaattg 180  
 ctgaataggc acagagggca cctgtacacc ttcagaccag tctgcaacct caggctgagt 240  
 agcagtgaac tcaggagcgg gagcagtgca ttcaccctga aattcctcct tggtaactgc 300  
 cttctcagca gcagcctgct cttctttttc aatctcttca ggatctctgt agaagtacag 360  
 atcaggcatg acctcccatg ggtgttcacg ggaaatggtg ccacgcatgc gcagaacttc 420  
 ccgagccagc atccaccaca ttaaaccac tgagttagct cccttgttgt tgcattggat 480  
 ggcaatgtcc acatagcgca gaggagaatc tgtgttacac agcgcaatgg taggtagggt 540  
 aacataagat gcctccgtga gaggcgaagg ggcggcgagg cccgggcctg gcccgatatg 600  
 gtccttggcg gcctagacta ggcgctcgt gtatggtgag cccagggag gcggatctgg 660  
 gccccagaa ggacacccgc ctggatttgc cccgtagccc ggcccgggccc cctcgggagc 720  
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 cacacatgta agattcaaga gtttgccgac ctaactgaag ttgaaacttt cggttttcag 1440  
 ggggaagctc tgagctcact gtgtgcaact agcgatgtca ccatttctac ctgccacgag 1500  
 ttggtgaagg ttgggactcg actggtgttt gatcacgatg ggaaaatcat ccaggaaacc 1560  
 ccctaccccc accccagagg gaccacagtc agcgtgaagc agttattttc tacgctacct 1620  
 gtgcgccata aggaatttca aaggaatatt aagaagacgt gcctgcttcc ccttcgcctt 1680  
 ctgccgtgat tgtcagtttc ctgaggcctc cccagccatg cttcctgtac agcctgcaga 1740  
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<210> 20  
 <211> 264

<212> PRT  
<213> Homo sapiens

<400> 20

Met Cys Pro Trp Arg Pro Arg Leu Gly Arg Arg Cys Met Val Ser Pro  
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Arg Glu Ala Asp Leu Gly Pro Gln Lys Asp Thr Arg Leu Asp Leu Pro  
20 25 30

Arg Ser Pro Ala Arg Ala Pro Arg Glu Gln Asn Ser Leu Gly Glu Val  
35 40 45

Asp Arg Arg Gly Pro Arg Glu Gln Thr Arg Ala Pro Ala Thr Ala Ala  
50 55 60

Pro Pro Arg Pro Leu Gly Ser Arg Gly Ala Glu Ala Ala Glu Pro Gln  
65 70 75 80

Glu Gly Leu Ser Ala Thr Val Ser Ala Cys Phe Gln Glu Gln Gln Glu  
85 90 95

Met Asn Thr Leu Gln Gly Pro Val Ser Phe Lys Asp Val Ala Val Asp  
100 105 110

Phe Thr Gln Glu Glu Trp Arg Gln Leu Asp Pro Asp Glu Lys Ile Ala  
115 120 125

Tyr Gly Asp Val Met Leu Glu Asn Tyr Ser His Leu Val Ser Val Gly  
130 135 140

Tyr Asp Tyr His Gln Ala Lys His His His Gly Val Glu Val Lys Glu  
145 150 155 160

Val Glu Gln Gly Glu Glu Pro Trp Ile Met Glu Gly Glu Phe Pro Cys  
165 170 175

Gln His Ser Pro Glu Pro Ala Lys Ala Ile Lys Pro Ile Asp Arg Lys  
180 185 190

Ser Val His Gln Ile Cys Ser Gly Pro Val Val Leu Ser Leu Ser Thr  
195 200 205

Ala Val Lys Glu Leu Val Glu Asn Ser Leu Asp Ala Gly Ala Thr Asn  
210 215 220

Ile Asp Leu Lys Leu Lys Asp Tyr Gly Val Asp Leu Ile Glu Val Ser  
225 230 235 240

Asp Asn Gly Cys Gly Val Glu Glu Glu Asn Phe Glu Gly Leu Ile Ser  
 245 250 255

Phe Ser Ser Glu Thr Ser His Met  
 260

<210> 21  
 <211> 795  
 <212> DNA  
 <213> Homo sapiens

<400> 21  
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 gagcagaaca gccttgggtga ggtggacagg aggggacctc gcgagcagac gcgcgcgcca 180  
 gcgacagcag ccccgccccg gcctctcggg agccgggggg cagaggctgc ggagccccag 240  
 gaggggtctat cagccacagt ctctgcatgt ttccaagagc aacaggaaat gaacacattg 300  
 cagggggccag tgtcattcaa agatgtggct gtggatttca cccaggagga gtggcggcaa 360  
 ctggaccctg atgagaagat agcatacggg gatgtgatgt tggagaacta cagccatcta 420  
 gtttctgtgg ggtatgatta tcaccaagcc aaacatcatc atggagtgga ggtgaaggaa 480  
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 gaacctgcta aggccatcaa acctattgat cggaagtcag tccatcagat ttgctctggg 600  
 ccagtggtag tgagtctaag cactgcagtg aaggagttag tagaaaacag tctggatgct 660  
 ggtgccacta atattgatct aaagcttaag gactatggag tggatctcat tgaagtttca 720  
 gacaatggat gtggggtaga agaagaaaac tttgaaggct taatctcttt cagctctgaa 780  
 acatcacaca tgtaa 795

<210> 22  
 <211> 264  
 <212> PRT  
 <213> Homo sapiens

<400> 22

Met Cys Pro Trp Arg Pro Arg Leu Gly Arg Arg Cys Met Val Ser Pro  
 1 5 10 15

Arg Glu Ala Asp Leu Gly Pro Gln Lys Asp Thr Arg Leu Asp Leu Pro  
 20 25 30

Arg Ser Pro Ala Arg Ala Pro Arg Glu Gln Asn Ser Leu Gly Glu Val  
 35 40 45

Asp Arg Arg Gly Pro Arg Glu Gln Thr Arg Ala Pro Ala Thr Ala Ala

50

55

60

Pro Pro Arg Pro Leu Gly Ser Arg Gly Ala Glu Ala Ala Glu Pro Gln  
65 70 75 80

Glu Gly Leu Ser Ala Thr Val Ser Ala Cys Phe Gln Glu Gln Gln Glu  
85 90 95

Met Asn Thr Leu Gln Gly Pro Val Ser Phe Lys Asp Val Ala Val Asp  
100 105 110

Phe Thr Gln Glu Glu Trp Arg Gln Leu Asp Pro Asp Glu Lys Ile Ala  
115 120 125

Tyr Gly Asp Val Met Leu Glu Asn Tyr Ser His Leu Val Ser Val Gly  
130 135 140

Tyr Asp Tyr His Gln Ala Lys His His His Gly Val Glu Val Lys Glu  
145 150 155 160

Val Glu Gln Gly Glu Glu Pro Trp Ile Met Glu Gly Glu Phe Pro Cys  
165 170 175

Gln His Ser Pro Glu Pro Ala Lys Ala Ile Lys Pro Ile Asp Arg Lys  
180 185 190

Ser Val His Gln Ile Cys Ser Gly Pro Val Val Leu Ser Leu Ser Thr  
195 200 205

Ala Val Lys Glu Leu Val Glu Asn Ser Leu Asp Ala Gly Ala Thr Asn  
210 215 220

Ile Asp Leu Lys Leu Lys Asp Tyr Gly Val Asp Leu Ile Glu Val Ser  
225 230 235 240

Asp Asn Gly Cys Gly Val Glu Glu Glu Asn Phe Glu Gly Leu Ile Ser  
245 250 255

Phe Ser Ser Glu Thr Ser His Met  
260

<210> 23

<211> 30

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic oligonucleotide primer

<400> 23

acgcatatgg agcgagctga gagctcgagt

30

<210> 24  
<211> 75  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic oligonucleotide primer

<400> 24  
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aaccttcgcc gatgc 75

<210> 25  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic oligonucleotide primer

<400> 25  
acgcatatgt gtccttggcg gcctaga 27

<210> 26  
<211> 75  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic oligonucleotide primer

<400> 26  
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tgatgtttca gagct 75

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<211> 49  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic oligonucleotide primer

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<223> corresponds to the first nucleotide of the first codon of the target mismatch repair gene

<220>  
<221> misc\_feature  
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<220>  
 <221> misc\_feature  
 <222> (37)..(37)  
 <223> corresponds to the third nucleotide of the first codon of the target mismatch repair gene

<220>  
 <221> misc\_feature  
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<220>  
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<220>  
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<220>  
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<220>  
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<220>  
 <221> misc\_feature  
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 <223> corresponds to the first nucleotide of the fifth codon of the target mismatch repair gene

<220>  
 <221> misc\_feature  
 <222> (48)..(48)  
 <223> corresponds to the second nucleotide of the fifth codon of the target mismatch repair gene

<220>  
 <221> misc\_feature  
 <222> (49)..(49)  
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<400> 27  
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<210> 28  
 <211> 4290  
 <212> DNA  
 <213> Homo sapiens

<400> 28  
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 gtggctgtca gggatgaatat ggaaaccttc caagttcaag tgatagacaa tggatttggg 180  
 atggggagtg atgatgtaga gaaagtggga aatcgttatt tcaccagtaa atgccactcg 240  
 gtacaggact tggagaatcc aaggttttat ggtttccgag gagaggcctt ggcaaatatt 300  
 gctgacatgg ccagtgtgtg ggaaatttcg tccaagaaaa acaggacaat gaaaactttt 360  
 gtgaaactgt ttcagagtgg aaaagccctg aaagcttggtg aagctgatgt gactagagca 420  
 agcgtggga ctactgtaac agtgtataac ctattttacc agcttcctgt aaggaggaaa 480  
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 atgcaccctt ccatttcttt ctctttgaga aatgatgttt ctggttccat gggtcttcag 600  
 ctccctaaaa ccaaagacgt atgttccga ttttgtcaaa tttatggatt gggaaagtcc 660  
 caaaagctaa gagaaataag ttttaaatat aaagagtttg agcttagtgg ctatatcagc 720  
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aggacaaagc tacataaact cattgacttt ttattaagga aagaaagtat tatatgcaag	840
ccaaagaatg gtcccaccag taggcctg aattcaagtc ttcggcaccg gtctacccca	900
gaactctatg gcatatatgt aattaatgtg cagtgccaat tctgtgagta tgatgtgtgc	960
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caggaaggag tgaaaatgtt tttaaagcaa gaaaaattat ttgtggaatt atcaggtgag	1080
gatattaagg aatttagtga agataatggt tttagtttat ttgatgctac tcttcagaag	1140
cgtgtgactt ccgatgagag gagcaatttc caggaagcat gtaataatat tttagattcc	1200
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gctggagaaa atgagaaaca taaaaaatct ttcttggaac atagctcttt agaaaatccg	1500
tgtggaacca gtttagaaat gtttttaagc ctttttcaga caccatgtca ctttgaggag	1560
agtgggcagg atctagaaat atggaaagaa agtactactg ttaatggcat ggctgccaac	1620
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actgaaacag aacattcatt taaaaattat gttagacctg gtcccacacg tgcccaagaa	1920
acatttgga atagaacacg tcattcagtt gaaactccag acatcaaaga tttagccagc	1980
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tatgggctag agaatgaacc tacagcaact tatacaatgt tttctgcttt tcaggaaggt	2100
agcaaaaaat cacaacaga ttgcatatta tctgatacat cccctcttt cccctggtat	2160
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tatgggaagg ttgaaaatcc tctggataca gaagtagagg aaagtaatgg agtcactacc	2340
aatctcagtc ttcaagttga acctgacatt ctgctgaagg acaagaaccg cttagagaac	2400
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Glu Asp Tyr Phe Gln Val Ile Asp Asn Gly Cys Gly Ile Ser Pro Thr  
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Asn Phe Lys Val Cys Val Gln Ile Leu Arg Arg Thr Phe Asp Val Leu  
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Ala Leu Lys His His Thr Ser Lys Leu Glu Asp Phe Thr Asp Leu Leu  
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Lys Thr Ala Arg Gln Ile Gly Thr Thr Val Thr Val Arg Lys Leu Phe  
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Lys Gly Val Arg Phe Val Cys Ser Asn Thr Thr Gly Lys Asn Pro Lys  
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Arg Asp Asp Leu Val Leu Leu Gly Glu Arg Tyr Ala Thr Ser Lys Phe  
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Gly Glu Ala Leu Ala Ser Ile Ser Asp Ile Ser Leu Leu Glu Val Arg  
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Ser Lys Cys Leu His Leu Gly Ile Asp Asp Asp Arg Lys Asp Ser Gly  
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Thr Thr Val Thr Val Arg Asp Leu Phe Tyr Ser Gln Pro Val Arg Arg  
145 150 155 160

Lys Tyr Met Gln Ser Ser Pro Lys Lys Val Leu Glu Ser Ile Lys Lys  
165 170 175

Cys Val Phe Arg Ile Ala Leu Val His Ser Asn Val Ser Phe Ser Val  
180 185 190

Leu Asp Ile Glu Ser Asp Glu Glu Leu Phe Gln Thr Asn Pro Ser Ser  
195 200 205

Ser Ala Phe Ser Leu Leu Met Arg Asp Ala Gly Thr Glu Ala Val Asn  
210 215 220

Ser Leu Cys Lys Val Asn Val Thr Asp Gly Met Leu Asn Val Ser Gly  
225 230 235 240

Phe Glu Cys Ala Asp Asp Trp Lys Pro Thr Asp Gly Gln Gln Thr Gly  
245 250 255

Arg Arg Asn Arg Leu Gln Ser Asn Pro Gly Tyr Ile Leu Cys Ile Ala  
260 265 270

Cys Pro Arg Arg Leu Tyr Glu Phe Ser Phe Glu Pro Ser Lys Thr His  
275 280 285

Val Glu Phe Lys Lys Trp Gly Pro Val Leu Ala Phe Ile Glu Arg Ile  
290 295 300

Thr Leu Ala Asn Trp Lys Lys Asp Arg Ile Leu Glu Leu Phe Asp Gly  
305 310 315 320

Gly Ala Asp Ile Leu Ala Lys Gly Asp Arg Gln Asp Leu Ile Asp Asp  
325 330 335

Lys Ile Arg Leu Gln Asn Gly Ser Leu Phe Ser Ile Leu His Phe Leu  
340 345 350

Asp Ala Asp Trp Pro Glu Ala Met Glu Pro Ala Lys Lys Lys Leu Lys  
355 360 365

Arg Ser Asn Asp His Ala Pro Cys Ser Ser Leu Leu Phe Pro Ser Ala  
370 375 380

Asp Phe Lys Gln Asp Gly Asp Tyr Phe Ser Pro Arg Lys Asp Val Trp  
385 390 395 400

Ser Pro Glu Cys Glu Val Glu Leu Lys Ile Gln Asn Pro Lys Glu Gln  
405 410 415

Gly Thr Val Ala Gly Phe Glu Ser Arg Thr Asp Ser Leu Leu Gln Ser  
420 425 430

Arg Asp Ile Glu Met Gln Thr Asn Glu Asp Phe Pro Gln Val Thr Asp  
435 440 445

Leu Leu Glu Thr Ser Leu Val Ala Asp Ser Lys Cys Arg Lys Gln Phé  
450 455 460

Leu Thr Arg Cys Gln Ile Thr Thr Pro Val Asn Ile Asn His Asp Phe  
465 470 475 480

Met Lys Asp Ser Asp Val Leu Asn Phe Gln Phe Gln Gly Leu Lys Asp  
485 490 495

Glu Leu Asp Val Ser Asn Cys Ile Gly Lys His Leu Leu Arg Gly Cys  
500 505 510

Ser Ser Arg Val Ser Leu Thr Phe His Glu Pro Lys Leu Ser His Val  
515 520 525

Glu Gly Tyr Glu Ser Val Val Pro Met Ile Pro Asn Glu Lys Gln Ser  
530 535 540

Ser Pro Arg Val Leu Glu Thr Arg Glu Gly Gly Ser Tyr Cys Asp Val  
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Tyr Ser Asp Lys Thr Pro Asp Cys Ser Leu Gly Ser Ser Trp Gln Asp  
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Thr Asp Trp Phe Thr Pro Gln Cys Ser Ser Asp Arg Gly Cys Val Gly  
580 585 590

Ile Gly Glu Asp Phe Asn Ile Thr Pro Ile Asp Thr Ala Glu Phe Asp  
595 600 605

Ser Tyr Asp Glu Lys Val Gly Ser Lys Lys Tyr Leu Ser Ser Val Asn  
610 615 620

Val Gly Ser Ser Val Thr Gly Ser Phe Cys Leu Ser Ser Glu Trp Ser  
625 630 635 640

Pro Met Tyr Ser Thr Pro Ser Ala Thr Lys Trp Glu Ser Glu Tyr Gln  
645 650 655

Lys Gly Cys Arg Ile Leu Glu Gln Ser Leu Arg Leu Gly Arg Met Pro  
660 665 670

Asp Pro Glu Phe Cys Phe Ser Ala Ala Asn Asn Ile Lys Phe Asp His  
675 680 685

Glu Val Ile Pro Glu Met Asp Cys Cys Glu Thr Gly Thr Asp Ser Phe  
690 695 700

Thr Ala Ile Gln Asn Cys Thr Gln Leu Ala Asp Lys Ile Cys Lys Ser  
705 710 715 720

Ser Trp Gly His Ala Asp Asp Val Arg Ile Asp Gln Tyr Ser Ile Arg  
725 730 735

Lys Glu Lys Phe Ser Tyr Met Asp Gly Thr Gln Asn Asn Ala Gly Lys  
740 745 750

Gln Arg Ser Lys Arg Ser Arg Ser Ala Pro Pro Phe Tyr Arg Glu Lys  
755 760 765

Lys Arg Phe Ile Ser Leu Ser Cys Lys Ser Asp Thr Lys Pro Lys Asn  
770 775 780

Ser Asp Pro Ser Glu Pro Asp Asp Leu Glu Cys Leu Thr Gln Pro Cys  
785 790 795 800

Asn Ala Ser Gln Met His Leu Lys Cys Ser Ile Leu Asp Asp Val Ser  
805 810 815

Tyr Asp His Ile Gln Glu Thr Glu Lys Arg Leu Ser Ser Ala Ser Asp  
820 825 830

Leu Lys Ala Ser Ala Gly Cys Arg Thr Val His Ser Glu Thr Gln Asp  
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Glu Asp Val His Glu Asp Phe Ser Ser Glu Glu Phe Leu Asp Pro Ile  
850 855 860

Lys Ser Thr Thr Lys Trp Arg His Asn Cys Ala Val Ser Gln Val Pro  
865 870 875 880

Lys Glu Ser His Glu Leu His Gly Gln Asp Gly Val Phe Asp Ile Ser  
885 890 895

Ser Gly Leu Leu His Leu Arg Ser Asp Glu Ser Leu Val Pro Glu Ser  
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Ile Asn Arg His Ser Leu Glu Asp Ala Lys Val Leu Gln Gln Val Asp  
915 920 925

Lys Lys Tyr Ile Pro Ile Val Ala Cys Gly Thr Val Ala Ile Val Asp  
930 935 940

Gln His Ala Ala Asp Glu Arg Ile Arg Leu Glu Glu Leu Arg Thr Lys  
945 950 955 960

Phe Ile Asn Asp Ala Leu Leu Ile Phe Val Leu Thr Leu Lys Val Leu  
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Pro Glu Met Gly Tyr Gln Leu Leu Gln Ser Tyr Ser Glu Gln Ile Arg  
 980 985 990

Asp Trp Gly Trp Ile Cys Asn Ile Thr Val Glu Gly Ser Thr Ser Phe  
 995 1000 1005

Lys Lys Asn Met Ser Ile Ile Gln Arg Lys Pro Thr Pro Ile Thr  
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Leu Asn Ala Val Pro Cys Ile Leu Gly Val Asn Leu Ser Asp Val  
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Asp Leu Leu Glu Phe Leu Gln Gln Leu Ala Asp Thr Asp Gly Ser  
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Ser Thr Ile Pro Pro Ser Val Leu Arg Val Leu Asn Ser Lys Ala  
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Cys Arg Gly Ala Ile Met Phe Gly Asp Ser Leu Leu Pro Ser Glu  
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Cys Ser Leu Ile Ile Asp Gly Leu Lys Gln Thr Ser Leu Cys Phe  
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Gln Cys Ala His Gly Arg Pro Thr Thr Val Pro Leu Val Asp Leu  
 1100 1105 1110

Lys Ala Leu His Lys Gln Ile Ala Lys Leu Ser Gly Arg Gln Val  
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Asp Ala Ser Val Arg Phe Ala Val Ser Lys Ser Val Asp Glu Val Arg  
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Gly .nr Asp Thr Pro Pro Glu Lys Val Pro Arg Arg Val Leu Pro Ser  
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Gly Phe Lys Pro Ala Glu Ser Ala Gly Asp Ala Ser Ser Leu Phe Ser  
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Asn Ile Met His Lys Phe Val Lys Val Asp Asp Arg Asp Cys Ser Gly  
100 105 110

Glu Arg Ser Arg Glu Asp Val Val Pro Leu Asn Asp Ser Ser Leu Cys  
115 120 125

Met Lys Ala Asn Asp Val Ile Pro Gln Phe Arg Ser Asn Asn Gly Lys  
130 135 140

Thr Gln Glu Arg Asn His Ala Phe Ser Phe Ser Gly Arg Ala Glu Leu  
145 150 155 160

Arg Ser Val Glu Asp Ile Gly Val Asp Gly Asp Val Pro Gly Pro Glu  
165 170 175

Thr Pro Gly Met Arg Pro Arg Ala Ser Arg Leu Lys Arg Val Leu Glu  
180 185 190

Asp Glu Met Thr Phe Lys Glu Asp Lys Val Pro Val Leu Asp Ser Asn  
195 200 205

Lys Arg Leu Lys Met Leu Gln Asp Pro Val Cys Gly Glu Lys Lys Glu  
210 215 220

Val Asn Glu Gly Thr Lys Phe Glu Trp Leu Glu Ser Ser Arg Ile Arg  
225 230 235 240

Asp Ala Asn Arg Arg Arg Pro Asp Asp Pro Leu Tyr Asp Arg Lys Thr  
245 250 255

Leu His Ile Pro Pro Asp Val Phe Lys Lys Met Ser Ala Ser Gln Lys  
260 265 270

Gln Tyr Trp Ser Val Lys Ser Glu Tyr Met Asp Ile Val Leu Phe Phe  
275 280 285

Lys Val Gly Lys Phe Tyr Glu Leu Tyr Glu Leu Asp Ala Glu Leu Gly  
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His Lys Glu Leu Asp Trp Lys Met Thr Met Ser Gly Val Gly Lys Cys  
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Arg Gln Val Gl<sub>325</sub> Ile Ser Glu Ser Gly Ile Asp Glu Ala Val Gln Lys<sub>330 335</sub>

Leu Leu Ala Arg Gly Tyr Lys Val Gly Arg Ile Glu Gln Leu Glu Thr<sub>340 345 350</sub>

Ser Asp Gln Ala Lys Ala Arg Gly Ala Asn Thr Ile Ile Pro Arg Lys<sub>355 360 365</sub>

Leu Val Gln Val Leu Thr Pro Ser Thr Ala Ser Glu Gly Asn Ile Gly<sub>370 375 380</sub>

Pro Asp Ala Val His Leu Leu Ala Ile Lys Glu Ile Lys Met Glu Leu<sub>385 390 395 400</sub>

Gln Lys Cys Ser Thr Val Tyr Gly Phe Ala Phe Val Asp Cys Ala Ala<sub>405 410 415</sub>

Leu Arg Phe Trp Val Gly Ser Ile Ser Asp Asp Ala Ser Cys Ala Ala<sub>420 425 430</sub>

Leu Gly Ala Leu Leu Met Gln Val Ser Pro Lys Glu Val Leu Tyr Asp<sub>435 440 445</sub>

Ser Lys Gly Leu Ser Arg Glu Ala Gln Lys Ala Leu Arg Lys Tyr Thr<sub>450 455 460</sub>

Leu Thr Gly Ser Thr Ala Val Gln Leu Ala Pro Val Pro Gln Val Met<sub>465 470 475 480</sub>

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Tyr Phe Lys Gly Ser Ser Glu Ser Trp Asn Cys Ala Val Asp Gly Leu<sub>500 505 510</sub>

Asn Glu Cys Asp Val Ala Leu Ser Ala Leu Gly Glu Leu Ile Asn His<sub>515 520 525</sub>

Leu Ser Arg Leu Lys Leu Glu Asp Val Leu Lys His Gly Asp Ile Phe<sub>530 535 540</sub>

Pro Tyr Gln Val Tyr Arg Gly Cys Leu Arg Ile Asp Gly Gln Thr Met<sub>545 550 555 560</sub>

Val Asn Leu Glu Ile Phe Asn Asn Ser Cys Asp Gly Gly Pro Ser Gly<sub>565 570 575</sub>

Thr Leu Tyr Lys Tyr Leu Asp Asn Cys Val Ser Pro Thr Gly Lys Arg  
580 585 590

Leu Leu Arg Asn Trp Ile Cys His Pro Leu Lys Asp Val Glu Ser Ile  
595 600 605

Asn Lys Arg Leu Asp Val Val Glu Glu Phe Thr Ala Asn Ser Glu Ser  
610 615 620

Met Gln Ile Thr Gly Gln Tyr Leu His Lys Leu Pro Asp Leu Glu Arg  
625 630 635 640

Leu Leu Gly Arg Ile Lys Ser Ser Val Arg Ser Ser Ala Ser Val Leu  
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Pro Ala Leu Leu Gly Lys Lys Val Leu Lys Gln Arg Val Lys Ala Phe  
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Gly Gln Ile Val Lys Gly Phe Arg Ser Gly Ile Asp Leu Leu Leu Ala  
675 680 685

Leu Gln Lys Glu Ser Asn Met Met Ser Leu Leu Tyr Lys Leu Cys Lys  
690 695 700

Leu Pro Ile Leu Val Gly Lys Ser Gly Leu Glu Leu Phe Leu Ser Gln  
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Phe Glu Ala Ala Ile Asp Ser Asp Phe Pro Asn Tyr Gln Asn Gln Asp  
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Val Thr Asp Glu Asn Ala Glu Thr Leu Thr Ile Leu Ile Glu Leu Phe  
740 745 750

Ile Glu Arg Ala Thr Gln Trp Ser Glu Val Ile His Thr Ile Ser Cys  
755 760 765

Leu Asp Val Leu Arg Ser Phe Ala Ile Ala Ala Ser Leu Ser Ala Gly  
770 775 780

Ser Met Ala Arg Pro Val Ile Phe Pro Glu Ser Glu Ala Thr Asp Gln  
785 790 795 800

Asn Gln Lys Thr Lys Gly Pro Ile Leu Lys Ile Gln Gly Leu Trp His  
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Pro Phe Ala Val Ala Ala Asp Gly Gln Leu Pro Val Pro Asn Asp Ile  
820 825 830

Leu Leu Gly Glu Ala Arg Arg Ser S Gly Ser Ile His Pro Arg Ser  
835 840 845

Leu Leu Leu Thr Gly Pro Asn Met Gly Gly Lys Ser Thr Leu Leu Arg  
850 855 860

Ala Thr Cys Leu Ala Val Ile Phe Ala Gln Leu Gly Cys Tyr Val Pro  
865 870 875 880

Cys Glu Ser Cys Glu Ile Ser Leu Val Asp Thr Ile Phe Thr Arg Leu  
885 890 895

Gly Ala Ser Asp Arg Ile Met Thr Gly Glu Ser Thr Phe Leu Val Glu  
900 905 910

Cys Thr Glu Thr Ala Ser Val Leu Gln Asn Ala Thr Gln Asp Ser Leu  
915 920 925

Val Ile Leu Asp Glu Leu Gly Arg Gly Thr Ser Thr Phe Asp Gly Tyr  
930 935 940

Ala Ile Ala Tyr Ser Val Phe Arg His Leu Val Glu Lys Val Gln Cys  
945 950 955 960

Arg Met Leu Phe Ala Thr His Tyr His Pro Leu Thr Lys Glu Phe Ala  
965 970 975

Ser His Pro Arg Val Thr Ser Lys His Met Ala Cys Ala Phe Lys Ser  
980 985 990

Arg Ser Asp Tyr Gln Pro Arg Gly Cys Asp Gln Asp Leu Val Phe Leu  
995 1000 1005

Tyr Arg Leu Thr Glu Gly Ala Cys Pro Glu Ser Tyr Gly Leu Gln  
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Val Ala Leu Met Ala Gly Ile Pro Asn Gln Val Val Glu Thr Ala  
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Ser Gly Ala Ala Gln Ala Met Lys Arg Ser Ile Gly Glu Asn Phe  
1040 1045 1050

Lys Ser Ser Glu Leu Arg Ser Glu Phe Ser Ser Leu His Glu Asp  
1055 1060 1065

Trp Leu Lys Ser Leu Val Gly Ile Ser Arg Val Ala His Asn Asn  
1070 1075 1080

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His Glu Ile Lys Ser Ser Tyr Cys Val Pro Lys  
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Leu Gly Asn Arg Gln Thr Pro Thr Leu Gly Asn Arg Gln Thr Pro Arg  
35 40 45

Leu Gly Ile His Ala Arg Pro Arg Arg Arg Ala Thr Thr Ser Leu Leu  
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Thr Leu Leu Leu Ala Phe Gly Lys Asn Ala Val Arg Cys Ala Leu Ile  
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Gly Pro Gly Ser Leu Thr Ser Arg Thr Arg Pro Leu Thr Glu Pro Leu  
85 90 95

Gly Glu Lys Glu Arg Arg Glu Val Phe Phe Pro Pro Arg Pro Glu Arg  
100 105 110

Val Glu His Asn Val Glu Ser Ser Arg Trp Glu Pro Arg Arg Arg Gly  
115 120 125

Ala Cys Gly Ser Arg Gly Gly Asn Phe Pro Ser Pro Arg Gly Gly Ser  
130 135 140

Gly Val Ala Ser Leu Glu Arg Ala Glu Asn Ser Ser Thr Glu Pro Ala  
145 150 155 160

Lys Ala Ile Lys Pro Ile Asp Arg Lys Ser Val His Gln Ile Cys Ser  
165 170 175

Gly Pro Val Val Pro Ser Leu Arg Pro Asn Ala Val Lys Glu Leu Val  
180 185 190

Glu Asn Ser Leu Asp Ala Gly Ala Thr Asn Val Asp Leu Lys Leu Lys  
195 200 205

Asp Tyr Gly Val Asp Leu Ile Glu Val Ser Gly Asn Gly Cys Gly Val  
210 215 220

Glu Glu Glu Asn Phe Glu Gly Phe Thr Leu Lys His His Thr Cys Lys  
225 230 235 240

Ile Gln Glu Phe Ala Asp Leu Thr Gln Val Glu Thr Phe Gly Phe Arg  
245 250 255

Gly Glu Ala Leu Ser Ser Leu Cys Ala Leu Ser Asp Val Thr Ile Ser  
260 265 270

Thr Cys Arg Val Ser Ala Lys Val Gly Thr Arg Leu Val Phe Asp His  
275 280 285

Tyr Gly Lys Ile Ile Gln Lys Thr Pro Tyr Pro Arg Pro Arg Gly Met  
290 295 300

Thr Val Ser Val Lys Gln Leu Phe Ser Thr Leu Pro Val His His Lys  
305 310 315 320

Glu Phe Gln Arg Asn Ile Lys Lys Lys Arg Ala Cys Phe Pro Phe Ala  
325 330 335

Phe Cys Arg Asp Cys Gln Phe Pro Glu Ala Ser Pro Ala Met Leu Pro  
340 345 350

Val Gln Pro Val Glu Leu Thr Pro Arg Ser Thr Pro Pro His Pro Cys  
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Pro Gly Ser Ser Arg  
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Asp Arg Arg Gly Pro Arg Glu Gln Thr Arg Ala Pro Ala Thr Ala Ala  
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Pro Pro Arg Pro Leu Gly Ser Arg Gly Ala Glu Ala Ala Glu Pro Gln  
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Glu Gly Leu Ser Ala Thr Val Ser Ala Cys Phe Gln Glu Gln Gln Glu  
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Met Asn Thr Leu Gln Gly Pro Val Ser Phe Lys Asp Val Ala Val Asp  
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Phe Thr Gln Glu Glu Trp Arg Gln Leu Asp Pro Asp Glu Lys Ile Ala  
115 120 125

Tyr Gly Asp Val Met Leu Glu Asn Tyr Ser His Leu Val Ser Val Gly  
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Tyr Asp Tyr His Gln Ala Lys His His His Gly Val Glu Val Lys Glu  
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Val Glu Gln Gly Glu Glu Pro Trp Ile Met Glu Gly Glu Phe Pro Cys  
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Gln His Ser Pro Glu Pro Ala Lys Ala Ile Lys Pro Ile Asp Arg Lys  
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Ser Val His Gln Ile Cys Ser Gly Pro Val Val Leu Ser Leu Ser Thr  
195 200 205

Ala Val Lys Glu Leu Val Glu Asn Ser Leu Asp Ala Gly Ala Thr Asn  
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Ile Asp Leu Lys Leu Lys Asp Tyr Gly Val Asp Leu Ile Glu Val Ser  
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Asp Asn Gly Cys Gly Val Glu Glu Glu Asn Phe Glu Gly Leu Ile Ser  
245 250 255

Phe Ser Ser Glu Thr Ser His Met  
260

105220 2692600